The effectiveness of Cognitive Behavioural Therapy for the treatment of fatigue in Multiple Sclerosis

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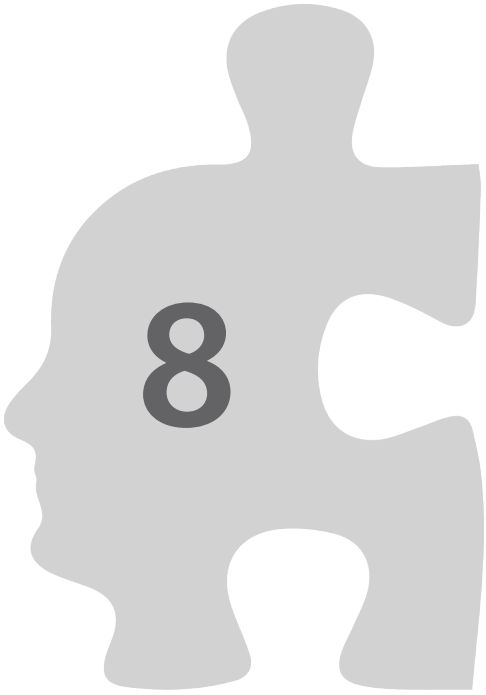

Cognitive Behavioural Therapy for MS-related fatigue explained: A longitudinal mediation analysis

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Submitted for publication

Abstract

Background Cognitive behavioural therapy (CBT) effectively reduces fatigue directly following treatment in patients with Multiple Sclerosis (MS), but little is known about the process of change during and after CBT.

Design Additional analysis of a randomized clinical trial.

Objective To investigate which psychological factors mediate the changes in fatigue during and after CBT.

Methods TREFAMS-CBT studied the effectiveness of a 16-week CBT treatment for MS-related fatigue. Ninety-one patients were randomized (44 to CBT, 47 to the MS-nurse intervention). Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from post-treatment to follow-up was studied separately using assessments at 16, 26 and 52 weeks. Proposed mediators were: changes in illness cognitions, general self-efficacy, coping styles, daytime sleepiness, concentration and physical activity, fear of disease progression, fatigue perceptions, depression and physical functioning. Mediators were separately analysed according to the product-of-coefficients approach. Confidence intervals were calculated with a bootstrap procedure.

Results During treatment the decrease in fatigue brought on by CBT was mediated by improved fatigue perceptions, increased physical activity, less sleepiness, less helplessness, and improved physical functioning. Post-treatment increases in fatigue levels were mediated by reduced physical activity, reduced concentration, and increased sleepiness.

Conclusion This study suggests that emphasis during treatment on fatigue perception/beliefs, physical activities, sleepiness, helplessness and physical functioning can benefit therapy. Maintaining treatment effects might be possible with treatments that lead to long-term maintenance of acquired habits regarding physical activity levels, concentration and sleep-wake patterns.

Introduction

Multiple Sclerosis is a neurodegenerative disease with clinical manifestations in the motor, visual, sensory and autonomic system, although symptoms may also occur in many other systems.[1] Many symptoms show a gradual increase in prevalence and severity.[2] One prevalent symptom in MS is fatigue, which is present in around 80% of patients in the first year of diagnosis.[1,2]

MS-related fatigue can have widespread effects on many domains of a person's life,[3-5] and can lead to problems in societal participation, e.g. contacts with family or friends, or maintaining employment. To improve understanding of MS-related fatigue several theoretical models have been developed.[6-13] These models all include the influence of biological, physical, psychological and environmental factors. Van Kessel et al. developed a cognitive behavioural model from which cognitive behavioural therapy (CBT) was developed.[12] CBT for MS-related fatigue aims to change the dysfunctional cognitions and behaviours that perpetuate or in some cases worsen fatigue. It involves challenging beliefs about fatigue and gradually increasing physical and social activity.[14]

In a recent randomized controlled trial (RCT) we reported that CBT has a positive short-term effect on MS-related fatigue,[Chapter 7] with the majority of patients no longer experiencing severe fatigue directly after treatment. However, fatigue severity was not significantly different from the control condition at one-year follow-up. Although little is still known about the process of change in MS-related fatigue during and after CBT, greater insight into underlying mechanisms is crucial to generating (more) positive outcomes during and after interventions.[15] One study that investigated factors mediating CBT effects on fatigue in patients with MS[16] found that effects were mainly mediated by *positive changes in beliefs* about fatigue. More research has been directed at identifying the factors mediating a reduction in fatigue following CBT for chronic fatigue syndrome.[17-20] These factors included less focus on fatigue,[17,20] increased sense of control over fatigue,[17] increased level of perceived activity and physical functioning,[17] fewer fear avoidance beliefs,[18,19] better social adjustment,[18] less catastrophizing,[19] decreased embarrassment avoidance,[19] no more limiting of activities,[19] and less all-or-nothing behaviour.[19]

To improve CBT for MS-related fatigue, we first need to understand which factors are related to the positive effect of CBT directly following treatment. As treatment effects do not persist, these insights may also help to improve long-term maintenance of positive effects. The aim of this study was to investigate which factors mediate the effect of CBT on MS-related fatigue *during* treatment and which factors mediate changes post-treatment

to 1-year follow-up. These factors were helplessness,[19] acceptance,[16] disease benefits,[16,19] general self-efficacy,[19] task-oriented coping,[19] emotion-oriented coping,[19] avoidance-oriented coping,[19] daytime sleepiness, reduction in concentration problems, increased level of physical activities,[18,19] fear of disease progression,[19] changes in the perception of fatigue,[16,19] reduction in depression and increased physical functioning.[17]

Methods

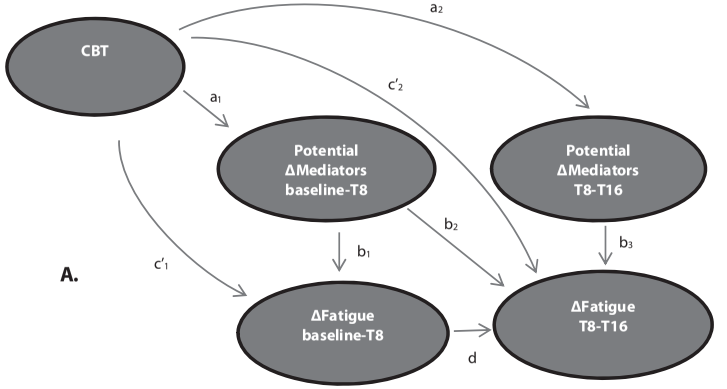
We performed an additional analysis of the TREFAMS-CBT study, which tested the effectiveness of CBT in MS-related fatigue.[Chapter 7] The complete TREFAMS-CBT study protocol has been published previously.[21] Patients were randomly assigned to CBT or to an MS-nurse control intervention. The TREFAMS-CBT trial revealed that MS-related fatigue decreased during and directly following CBT, but the effects on MS-related fatigue were diminished at follow-up. Therefore, we studied two mediation models in the current study: 1. during treatment, including baseline, 8-week and 16-week (i.e. post-intervention) data (see Figure 8.1A), and 2. after CBT, including 16-week data, 26-week data and 52-week data (see Figure 8.1B).[21]

Participants

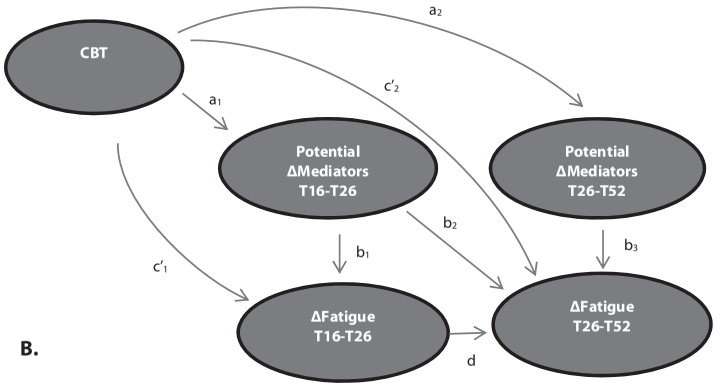
Patients with a definite MS diagnosis were included who were severely fatigued (Checklist of Individual Strength fatigue subscale score ≥35),[22] ambulatory (Expanded Disability Status Scale (EDSS) score ≤6.0),[23] had no signs of exacerbation, had not used a corticosteroid treatment within the past 3 months, no current infections, no anaemia, and with normal thyroid function. Exclusion criteria were signs of a clinical depression (a score >11 on the Hospital Anxiety and Depression Scale [HADS]),[24] severe comorbidity, primary sleep disorders, a non-pharmacological treatment for fatigue in the past three months, a pharmacological treatment for fatigue that was started in the past three months, or a current/recent pregnancy.

CBT and control intervention

The patients allocated to CBT received 12 sessions of face-to-face therapy. The sessions were spread over a 16-week period (8 sessions in the first 8 weeks, 4 sessions in the last



Path a_1: CBT -> ΔMediator $_{\text{baseline-T8}}$
Path a_2: CBT -> ΔMediator $_{\text{T8-T16}}$
Path b_1: ΔMediator $_{\text{baseline-T8}}$ -> ΔFatigue $_{\text{baseline-T8}}$
Path b_2: ΔMediator $_{\text{baseline-T8}}$ -> ΔFatigue $_{\text{T8-T16}}$
Path b_3: ΔMediator $_{\text{T8-T16}}$ -> ΔFatigue $_{\text{T8-T16}}$
Path c'_1: Direct relation CBT -> ΔFatigue $_{\text{baseline-T8}}$
Path c'_2: Direct relation CBT -> ΔFatigue $_{\text{T8-T16}}$
Path d: ΔFatigue $_{\text{baseline-T8}}$ -> ΔFatigue $_{\text{T8-T16}}$
Path M_1: Indirect relation a_1*b_1*d
Path M_2: Indirect relation a_1*b_2
Path M_3: Indirect relation a_2*b_3
Studied paths for the model of Figure 8.1A



Path a_1: CBT -> ΔMediator $_{\text{T16-T26}}$
Path a_2: CBT -> ΔMediator $_{\text{T26-T52}}$
Path b_1: ΔMediator $_{\text{T16-T26}}$ -> ΔFatigue $_{\text{T16-T26}}$
Path b_2: ΔMediator $_{\text{T16-T26}}$ ->ΔFatigue $_{\text{T26-T52}}$
Path b_3: ΔMediator $_{\text{T26-T52}}$ -> ΔFatigue $_{\text{T26-T52}}$
Path c'_1: Direct relation CBT -> ΔFatigue $_{\text{T16-T26}}$
Path c'_2: Direct relation CBT-> ΔFatigue $_{\text{T26-T52}}$
Path d: ΔFatigue $_{\text{T16-T26}}$ -> ΔFatigue $_{\text{T26-T52}}$
Path M_1: Indirect relation a_1*b_1*d
Path M_2: Indirect relation a_1*b_2
Path M_3: Indirect relation a_2*b_3
Studied paths for the model of Figure 8.1B

Figure 8.1 The effect of Cognitive Behavioural Therapy on fatigue with the potential mediators. **A.** During treatment. **B.** After treatment.

8 weeks). The CBT protocol was based on a cognitive behavioural model of MS-related fatigue which assumes that fatigue-related beliefs and behaviours perpetuate fatigue. The protocol consisted of 10 treatment modules (Appendix 3: CBT treatment modules): formulating goals, regulating sleep/wake pattern, changing beliefs regarding MS, changing beliefs regarding fatigue, reduce the focus on fatigue, regulation of physical, social, and mental activity, the role of the environment and how to handle pain. The CBT was patient-tailored: questionnaire scores and information from the intake session were used to determine which modules were indicated per patient. CBT therapists were state-certified healthcare psychologists who received a 3-day CBT course on the study protocol. Furthermore, they received supervision every other week from an experienced CBT therapist.

The control intervention consisted of 3 MS-nurse consultations of 45 minutes over a 16-week period. In this minimal intervention patients received written and oral information about MS-related fatigue, and they discussed their personal experiences in coping with fatigue and fatigue-related issues. More information about the CBT and the control intervention can be found elsewhere,[Chapter 7,21] Appendix 3: CBT-treatment modules, and Appendix 2: TREFAMS-Cognitive Behavioural Therapy.

Instruments

Primary outcome

Fatigue

The Checklist Individual Strength (CIS20r) subscale fatigue severity was used as a primary outcome.[22] Patients rated how much they agreed or disagreed with eight fatigue statements on a 7-point Likert scale. Fatigue scores range from 8 to 56 points, with higher scores representing greater fatigue. All patients in the present study had a score of 35 or higher before enrolment in the TREFAMS-study, which indicates severe fatigue. This questionnaire is considered valid for the measurement of fatigue in patients with MS.[13,22,25]

Studied mediators

Helplessness, acceptance and disease benefits

The Illness Cognitions Questionnaire (ICQ)-subscales helplessness, acceptance and disease benefits were used to measure illness cognitions.[26,27] These three subscales all consist of six questions, answered on a 4-point Likert-like scale (range 6–24). The

subscales focus on the meaning patients attribute to their disease. Higher scores represent more helplessness, acceptance and disease benefits. The complete ICQ questionnaire is considered valid and reliable.[26,27] These subscales were not specifically addressed during CBT but were partially handled in the TREFAMS-CBT module 'changing beliefs regarding MS'.

General self-efficacy

General self-efficacy was measured with the Dutch General Self-Efficacy Scale (GSES).[28] This questionnaire measures the patient's belief in their ability to perform difficult tasks in various domains of functioning in terms of taking appropriate action. This entails persistence when facing barriers, and recovery from setbacks.[29] The scale consists of 10 questions, answered on a 4-point scale (range 10–40). A higher score represents a higher level of self-efficacy. The questionnaire is reported to be valid.[29,30] General self-efficacy was not specifically addressed during treatment, but self-efficacy with respect to fatigue was part of the TREFAMS-CBT module 'changing beliefs regarding fatigue'.

Coping styles: task-oriented, emotion-oriented and avoidance-oriented

Coping styles were measured with the short form of the Coping Inventory for Stressful Situations (CISS21).[31] All three subscales consist of 7 items, and items were scored on a 1 (not at all) to 5 (very strong) point scale (range 7–35). Task-oriented coping is also called problem-solving coping, described as targeting stressful situations in practical ways that should consequently reduce stress. The emotion-oriented subscale focuses on negative emotions, for example worrying and blaming oneself. The avoidance-oriented subscale is about seeking distraction by seeking other people's company. Higher scores indicate a greater tendency to a certain coping style. The complete questionnaire is valid and reliable in Dutch patients with MS.[31,32] The coping styles are related to multiple CBT modules including changing beliefs regarding MS, reducing the focus on fatigue, regulation of physical, social, and mental activity, and the role of the environment.

Daytime sleepiness

Daytime sleepiness was measured with the valid and reliable Epworth Sleepiness Scale (ESS).[33] This questionnaire consists of 8 items, measured on a 0 to 3-point scale (range 0–24). The items measure wakefulness and the sleepiness during daytime activities. Higher scores indicate more daytime sleepiness.[33] Patients with a score >10 are advised

to consult a physician.[34] Daytime sleepiness was not specifically addressed during treatment; however, daytime sleepiness might be influenced by the regulating sleep/wake TREFAMS-CBT module.

Concentration and physical activities

Concentration and physical activities were measured using the identically named subscales of the CIS20r.[22] All items are answered on a 7-point Likert scale. The concentration subscale consists of 5 items (5–35) and the physical activities subscale consists of 3 items (3–21). Concentration is a treatment outcome of the TREFAMS-CBT module 'regulation of mental activity', while the physical activities subscale is related to the graded activity program that is part of the TREFAMS-CBT.

Fear of disease progression

Fear of disease progression was measured with the Fear of Progressions Questionnaire (FPQ), which consists of 34 items, divided over 4 subscales: affective relations, partnership/family, work, and loss of autonomy.[35] The items are answered on a five-point scale, ranging from never to very often. This questionnaire measures the amount of distress that fear of disease progression in chronic illnesses can cause. For the current study we used the total score, i.e. the sum of the four means per subscale, with a possible range of 0–20. The total score has high test-retest reliability and high internal consistency.[35] Fear of disease progression is addressed in the TREFAMS-CBT module 'changing beliefs regarding MS'.

Fatigue perceptions

Fatigue perceptions were measured with the modified Brief Illness Perception Questionnaire (BIPQ),[36] which consists of 7 items, answered on a 0–10 scale. For the current study, the word 'illness' was replaced with 'fatigue' to allow measurement of beliefs about MS-related fatigue rather than about the illness MS. Two items were excluded, since they were not relevant to fatigue perceptions.[16] The modified scale measures a patient's cognitive and emotional representation of their fatigue, which includes personal control, treatment control, coherence, concern and emotional responses. For the current study we used the total score, higher scores representing a more positive perception of fatigue. Perpetuating fatigue perceptions and behaviours were part of the TREFAMS-CBT modules 'changing beliefs regarding fatigue' and 'reduce the focus on fatigue'.

Depressive symptoms

The course of depressive symptoms during the one-year study participation was included as a potential mediator, since depression and fatigue are related.[37] The subscale depression of the HADS consists of 7 items, and participants had to choose one of four options that best reflected how depressed they felt in the past week. Internal consistency and test-retest reliability are considered good.[24] Depression (HADS-score >11) was used as an exclusion criterion for the TREFAMS-CBT trial.[21]

Physical functioning

The SF36-physical functioning subscale was used to measure perceived physical functioning. It consists of 10 questions, with the total score ranging from 0–100. Higher scores represent better physical functioning. The SF36-physical functioning is reliable and valid for measuring physical functioning in patients with MS.[38] Improved physical functioning is the goal of the TREFAMS-CBT module 'regulation of physical activity'.

Statistics

The demographics of the study population were analyzed using SPSS 22 for windows (SPSS Inc., Chicaco, IL). Visual inspection of histograms and normal probability plots were used to check whether normality assumptions of the individual variables were met.[39] The Mplus 7.11 software program was used to perform mediation analyses on the longitudinal trial data.

Mediation during treatment and mediation post-treatment was analysed in two separate mediation models which were analysed separately per potential mediator (Figure 8.1 A and B). The model was built in 2 steps. In step 1, the direct relation between CBT and $\Delta fatigue_{baseline-T8}$ and $\Delta fatigue_{T8-T16}$ was determined, i.e. without any mediators added to the model. In step 2, we used a lower triangular design (as displayed in Figure 8.1) to assess whether potential mediator variables mediated the relationship between CBT and the change in fatigue. For each potential mediator the coefficients depicted in Figure 8.1 were determined. The indirect effects of CBT on fatigue (Figure 8.1) were calculated based on the product-of-coefficients approach.[40,41] A bootstrap procedure with 5000 bootstrap re-samples was used to determine the 95% confidence intervals (CIs). Furthermore, the percentage of the effect that can be attributed to the mediating effect of the mediator was calculated by dividing the estimator of the mediated relation (Path M1/M2/M3) obtained in step 2 by the estimator c'_2 of the unmediated relation obtained in step 1, multiplied with 100. Factors were considered mediators when the indirect effect was significant.

Results

Of the 91 patients included, 44 (13 male, 31 female) were randomly allocated to CBT and 47 (8 male, 39 female) to the MS-nurse consultations. Baseline demographics are shown in Table 8.1. Table 8.2 includes a description of the observed results per study arm on fatigue and on the investigated mediators. Fatigue decreases considerably during the first 8 weeks in the CBT study group, after which fatigue stays stable until week 16. Over the long-term, the difference in fatigue severity between both conditions diminished.

Table 8.1 Baseline characteristics of the TREFAMS-CBT study population

Characteristic	CBT n=44 n (%)	MS-nurse n=47 n (%)
Gender		
Female	31 (70.5)	39 (83.0)
Age in years (mean, SD)	50.6 (8.3)	46.4 (11.6)
Time since diagnosis		
0–5 years	18 (40.9)	23 (48.9)
5–10 years	5 (11.4)	6 (12.8)
≥10 years	19 (43.2)	17 (36.2)
Unknown	2 (4.5)	1 (2.1)
Type of MS		
Relapsing Remitting	32 (72.7)	35 (74.5)
Primary Progressive	6 (13.6)	4 (8.5)
Secondary Progressive	5 (11.4)	7 (14.9)
Not specified	1 (2.3)	1(2.1)
Living situation		
Living with partner	34 (77.3)	33 (70.2)
Living without partner	10 (22.7)	13 (27.7)
Employment status		
Full-time	4 (9.1)	4 (8.5)
Part-time	16 (36.4)	18 (38.3)
Disability pension	9 (65.3)	9 (50.0)
Unemployed	20 (45.5)	19 (40.4)
Disability pension	17 (85.0)	15 (75.0)
Retirement	1 (2.3)	3 (6.4)
Study	1 (2.3)	2 (4.3)
Unknown	2 (4.6)	1 (2.1)

Table 8.2 Descriptives of the dependent variable fatigue and the mediator variables per intervention group during the one-year participation in the TREFAMS-CBT trial

			Baseline	T8	T16 (post-intervention)	T26	T52	Possible range
	Questionnaire	Intervention	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	
Dependent variable								
Fatigue	CIS20r	CBT	42.86 (8.46) 27–56	33.50 (10.39) 13–51	33.97 (11.20) 18–56	36.90 (12.13) 16–56	38.92 (9.69) 12–54	8–56
		Control	44.17 (6.03) 28–56	41.03 (8.33) 20–55	40.34 (8.15) 20–56	40.86 (7.80) 19–53	39.54 (9.01) 19–52	
Studied mediators								
Helplessness	ICQ	CBT	13.20 (3.97) 7–23	11.18 (2.91) 6–17	11.40 (3.50) 7–20	11.57 (3.59) 7–22	12.21 (3.61) 6–24	6–24
		Control	12.61 (3.71) 6–21	11.84 (2.96) 7–18)	11.06 (3.14) 6–18	11.46 (3.02) 6–18	11.41 (3.06) 6–19	
Acceptance*	ICQ	CBT	15.02 (4.32) 6–23	16.61 (4.22) 9–24	16.54 (4.13) 6–24	16.34 (4.18) 7–24	16.44 (4.49) 6–24	6–24
		Control	14.41 (4.04) 6–24	15.24 (3.93) 7–24	15.56 (4.18) 7–23	15.97 (3.84) 7–23	16.11 (4.05) 9–24	
Disease benefits*	ICQ	CBT	14.75 (4.86) 6–24	15.66 (3.65) 10–23	15.23 (4.46) 8–24	15.18 (4.50) 6–24	15.49 (4.46) 6–24	6–24
		Control	14.37 (4.11) 6–24	13.97 (4.78) 7–24	13.94 (4.65) 6–24	14.09 (4.71) 7–24	14.22 (4.30) 6–24	
General self-efficacy*	GSES	CBT	28.73 (5.61) 11–40	29.89 (4.94) 17–39	29.66 (5.60) 10–38	30.05 (4.97) 15–40	30.08 (5.19) 10–40	10–40
		Control	30.85 (4.54) 21–40	31.39 (4.09) 18–40	30.00 (5.57) 15–40	31.51 (4.53) 24–40	31.92 (5.06) 24–40	

Table 8.2 continues on next page

Table 8.2 *Continued*

			Baseline	T8	T16 (post-intervention)	T26	T52	Possible range
	Questionnaire	Intervention	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	
Task-oriented coping**	CISS21	CBT	23.23 (5.71) 7–32	23.39 (5.30) 9–35	23.78 (4.99) 11–34	24.89 (4.69) 14–34	24.00 (4.31) 15–33	7–35
		Control	24.61 (4.60) 17–34	24.95 (4.32) 11–35	23.97 (5.84) 9–34	24.97 (5.21) 11–34	25.49 (4.58) 17–35	
Emotion-oriented coping**	CISS21	CBT	18.50 (7.04) 8–30	16.84 (5.96) 7–33	18.14 (5.90) 9–31	16.92 (5.67) 7–30	16.46 (5.97) 8–32	7–35
		Control	18.13 (5.54) 8–30	16.34 (6.11) 7–30	16.11 (4.87) 7–25	16.43 (5.42) 8–25	15.92 (5.92) 7–28	
Avoidance-oriented coping**	CISS21	CBT	16.68 (5.16) 7–31	16.97 (4.46) 7–24	16.81 (4.72) 10–28	16.34 (5.18) 7–30	16.21 (5.39) 7–28	7–35
		Control	18.48 (5.98) 7–29	19.92 (5.77) 9–33	18.97 (4.61) 7–26	19.00 (4.59) 7–28	19.92 (5.76) 7–34	
Daytime sleepiness	ESS	CBT	8.77 (5.89) 0–21	6.50 (5.01) 1–17	7.49 (5.92) 0–19	8.16 (5.93) 0–20	7.00 (5.04) 0–20	0–24
		Control	9.67 (4.96) 1–19	9.58 (5.63) 0–23	9.39 (5.60) 1–19	9.19 (5.59) 1–18	8.38 (5.29) 0–21	
Concentration	CIS20r	CBT	22.66 (8.50) 6–35	20.00 (8.14) 6–34	20.08 (7.65) 6–35	20.77 (7.41) 5–34	20.85 (6.96) 8–34	5–35
		Control	22.09 (6.55) 5–35	21.34 (6.19) 6–32	21.31 (7.33) 5–35	20.00 (6.50) 8–32	21.37 (8.04) 5–33	
Physical activities	CIS20r	CBT	13.39 (5.59) 3–21	10.34 (4.89) 3–21	10.54 (5.25) 3–21	11.62 (4.71) 5–21	12.95 (4.99) 3–21	3–21
		Control	13.17 (3.64) 6–21	12.42 (3.58) 5–20	12.39 (4.31) 5–21	11.61 (4.57) 4–21	12.14 (4.43) 3–20	

Table 8.2 continues on next page

Table 8.2 *Continued*

			Baseline	T8	T16 (post-intervention)	T26	T52	Possible range
	Questionnaire	Intervention	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	Mean (SD) range	
Fear of disease progression	FPQ	CBT	9.69 (2.53) 4.43–18.09	8.72 (2.64) 5.57–20.00	9.31 (2.56) 5.09–18.23	8.54 (2.54) 4.53–18.53	8.57 (2.70) 5.11–17.93	0–20
		Control	9.78 (2.57) 5.08–15.27	8.94 (2.61) 4.51–14.49	9.17 (2.22) 4.67–13.54	8.95 (2.31) 4.75–14.20	8.55 (2.32) 4.30–12.80	
Fatigue perception	mBIPQ	CBT	45.29 (7.23) 31–60	37.00 (8.87) 21–60	36.97 (8.82) 16–57	36.79 (8.58) 18–58	38.82 (8.88) 18–61	0–70
		Control	44.87 (7.38) 28–60	43.05 (7.76) 15–56	43.89 (7.03) 24–61	43.68 (5.55) 31–56	43.03 (8.55) 24–62	
Depression	HADS	CBT	5.58 (3.60) 0–14	4.05 (3.26) 0–17	4.54 (4.17) 0–17	4.92 (3.68) 1–14	5.08 (3.84) 1–18	0–21***
		Control	4.78 (2.77) 1–11	4.37 (3.05) 0–12	3.42 (2.86) 0–13	4.17 (3.47) 0–15	4.31 (3.43) 1–15	
Physical functioning*	SF36	CBT	55.80 (22.10) 20–95	58.85 (21.47) 20–95	58.24 (24.84) 10–100	55.77 (23.66) 15–100	55.90 (22.33) 10–95	0–100
		Control	62.21 (20.44) 10–95	57.01 (23.33) 10–90	61.25 (20.15) 25–90	58.06 (21.66) 15–95	60.27 (22.01) 20–95	

* Higher values indicate a better outcomes.
** Higher values indicate a stronger tendency to this coping style.
*** During the intake patients were excluded with a HADS-score >11.
Abbreviations: mBIPQ, modified Brief Illness Perception Questionnaire; CIS20r, Checklist Individual Strength; CISS21, Coping Inventory for Stressful Situations; ESS, Epsworth Sleepiness Scale; FPQ, Fear of Progression Questionnaire; GSES, General Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; ICQ, Illness Cognitions Questionnaire; SF36, Short Form.

Table 8.3 Results of longitudinal mediation analysis during CBT treatment

	Estimator (95% CI)								Estimator (95% CI)			% Mediation*		
	a_1	a_2	b_1	c'_1	b_2	b_3	d	c'_2	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$
Step 1: Unmediated relation														
								2.45 -1.09;5.93						
Step 2: Relation with studied mediators														
Helplessness	1.24 -0.24;2.69	-0.92 -2.29;0.45	**0.84** **0.08;1.58**	**5.65** **1.37;9.71**	-0.12 -0.70;0.42	**0.83** **0.18;1.45**	**-0.48** **-0.65;-0.33**	**3.22** **0.08;6.46**	**-0.50** **-1.61;-0.03**	-0.15 -1.33;0.42	-0.77 -2.56;0.27	**20.4**	6.1	31.4
Acceptance	-0.92 -2.53;0.68	0.66 -0.75;2.01	-0.31 -1.04;0.39	**6.40** **1.95;10.65**	-0.30 -0.88;0.38	**-0.78** **-1.42;-0.02**	**-0.52** **-0.68;-0.37**	2.66 -0.84;6.05	-0.15 -1.04;0.13	0.27 -0.23;1.90	-0.52 -2.39;0.34	6.1	11.0	21.2
Disease benefits	-1.34 -2.99;0.36	0.62 -1.37;2.16	-0.39 -1.12;0.30	**6.16** **1.89;10.45**	-0.39 -0.85;0.08	**-0.92** **-1.67;-0.40**	**-0.53** **-0.68;-0.40**	2.57 -0.97;5.87	-0.28 -1.53;0.12	0.53 -0.07;2.16	-0.57 -2.94;0.96	11.4	21.6	23.3
General self-efficacy	-1.24 -2.84;0.38	-0.97 -2.90;0.58	-0.65 -1.41;0.04	**5.88** **1.59;10.14**	-0.39 -0.82;0.15	**-0.75** **-1.55;-0.35**	**-0.53** **-0.69;-0.38**	1.43 -1.99;4.65	-0.43 -1.71;0.04	0.48 -0.13;1.91	0.73 -0.50;2.20	17.6	19.6	29.8
Coping task-oriented	-0.47 -2.86;2.00	-0.91 -3.40;1.15	-0.38 -0.86;0.01	**6.50** **2.32;10.59**	0.10 -0.29;0.43	-0.25 -0.75;0.28	**-0.48** **-0.65;-0.33**	2.00 -1.34;5.37	-0.09 -0.75;0.34	-0.05 -0.89;0.31	0.23 -0.28;1.70	3.7	2.0	9.4
Coping emotion-oriented	-0.53 -2.94;2.06	-1.18 -3.72;1.31	0.10 -0.32;0.46	**6.74** **2.50;10.96**	0.05 -0.30;0.38	0.34 -0.05;0.74	**-0.54** **-0.71;-0.36**	3.03 -0.60;6.70	0.03 -0.17;0.56	-0.03 -0.84;0.32	-0.40 -1.97;0.28	1.2	1.2	16.3
Coping avoidance-oriented	0.50 -1.51;2.68	-0.67 -2.60;1.36	-0.03 -0.54;0.43	**6.70** **2.51;10.99**	**-0.50** **-0.81;-0.12**	-0.07 -0.52;0.47	**-0.50** **-0.67;-0.34**	2.72 -0.71;6.21	0.01 -0.20;0.41	-0.25 -1.71;0.65	0.05 -0.38;1.01	0.4	10.2	2.0

Table 8.3 continues on next page

Table 8.3 *Continued*

	Estimator (95% CI)								Estimator (95% CI)			% Mediation*		
	a_1	a_2	b_1	c'_1	b_2	b_3	d	c'_2	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$
Daytime sleepiness	**2.54** **1.04;4.10**	0.10 -1.52;1.71	0.58 -0.06;1.28	**5.21** **0.60;9.83**	**0.52** **0.03;1.10**	**0.68** **0.22;1.19**	**-0.55** **-0.71;-0.39**	1.07 -2.94;4.65	**-0.80** **-2.43;-0.05**	**1.32** **0.15;3.39**	0.07 -1.06;1.43	**32.7**	**53.9**	2.9
Concentration	2.00 -0.66;4.60	0.85 -1.64;3.35	**0.69** **0.21;1.09**	**5.31** **1.39;9.38**	**0.40** **0.06;0.82**	**0.72** **0.32;1.08**	**-0.53** **-0.69;-0.38**	1.26 -1.83;4.31	-0.76 -2.56;0.07	0.80 -0.15;2.63	0.61 -1.14;2.60	31.0	32.7	24.9
Physical activities	**2.63** **0.96;4.40**	0.08 -1.80;2.01	**1.02** **0.35;1.61**	4.01 -0.08;8.44	0.28 -0.17;0.70	**1.10** **0.74;1.52**	**-0.44** **-0.60;-0.31**	1.34 -1.44;4.21	**-1.18** **-2.78;-0.41**	0.73 -0.30;2.34	0.09 -2.11;2.22	**48.2**	29.8	3.7
Fear of disease progression	-0.10 -1.69;1.65	-0.23 -0.80;0.27	-0.12 -0.62;0.51	**6.73** **2.38;11.18**	-0.22 -0.75;0.30	-0.58 -2.50;1.06	-0.52 -0.69;0.36	2.55 -1.01;5.93	-0.01 -0.44;0.19	0.02 -0.37;0.96	0.13 -0.21;1.43	0.4	0.8	5.3
Fatigue perception	**6.91** **3.07;10.58**	1.99 -1.88;6.23	**0.50** **0.21;0.77**	3.25 -1.25;7.73	0.04 -0.16;0.23	**0.33** **0.06;0.55**	**-0.45** **-0.62;-0.29**	1.17 -2.22;4.62	**-1.55** **-3.50;-0.61**	0.25 -1.01;2.05	0.65 -0.45;2.46	**63.3**	3.9	26.5
Depression	-0.41 -1.66;0.85	-0.59 -2.27;0.97	-0.23 -1.05;0.57	**6.51** **2.15;11.00**	0.06 -0.81;0.83	0.72 -0.14;1.44	**-0.54** **-0.72;-0.37**	2.91 -0.57;6.43	-0.05 -0.76;0.15	-0.23 -0.80;0.39	-0.43 -2.44;0.63	2.0	9.4	17.6
Physical functioning	**-5.00** **-10.04;-0.26**	3.41 -2.03;9.43	**-0.34** **-0.57;-0.13**	**4.96** **1.02;8.84**	0.02 -0.12;0.20	**-0.16** **-0.30;-0.00**	**-0.47** **-0.63;-0.30**	2.85 -0.63;6.22	**-0.81** **-2.14;-0.15**	-0.09 -1.07;0.37	-0.54 -2.29;0.17	**33.1**	3.7	22.0

* Estimator of mediated relation ($Path_{M1/M2/M3}$) / estimator c'_2 of the unmediated relation*100%.

Table 8.4 Results of longitudinal mediation analysis after treatment

	Estimator (95% CI)								Estimator (95% CI)			% Mediation*		
	a_1	a_2	b_1	c'_1	b_2	b_3	d	c'_2	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$
Step 1: Unmediated relation														
								-6.49 **-11.33;-1.76**						
Step 2: Relation with studied mediators														
Helplessness	0.06 -1.00;1.14	-0.75 -2.05;0.50	0.37 -0.72;1.69	**-3.65** **-7.44;-0.33**	-0.35 -2.08;1.30	**1.76** **0.65;2.93**	**-0.67** **-0.92;-0.33**	**-5.14** **-9.05;-1.09**	-0.02 -0.81;0.35	-0.02 -1.46;0.71	-1.32 -4.68;0.64	0.3	0.3	20.3
Acceptance	0.40 -0.68;1.48	0.38 -1.00;1.62	-0.07 -0.84;0.78	**-3.64** **-7.21;-0.22**	**1.26** **0.09;2.56**	**-1.96** **-2.74;-1.05**	**-0.66** **-0.92;-0.32**	**-6.13** **-10.63;-1.95**	0.02 -0.25;0.53	0.51 -0.61;2.94	-0.74 -3.83;1.79	0.3	7.8	11.4
Disease benefits	-0.04 -1.35;1.22	-0.34 -1.95;1.15	-0.29 -0.96;0.37	**-3.65** **-7.32;-0.24**	0.12 -1.05;1.23	**-1.19** **-2.12;-0.24**	**-0.63** **-0.91;-0.18**	**-6.63** **-10.75;-2.40**	-0.01 -0.49;0.30	-0.00 -0.98;0.73	0.40 -1.29;3.17	0.2	0.0	6.2
General self-efficacy	0.24 -1.23;1.65	1.26 -0.33;2.98	-0.01 -0.55;0.66	**-3.66** **-7.28;-0.22**	0.39 -0.23;1.35	-0.72 -1.41;0.03	**-0.68** **-0.94;-0.31**	**-5.78** **-10.22;-1.96**	0.00 -0.31;0.42	0.09 -0.35;1.72	-0.91 -3.33;0.10	0.0	1.4	14.0
Coping task-oriented	-0.35 -2.11;1.34	1.09 -1.07;3.32	-0.19 -0.74;0.34	**-3.69** **-7.48;-0.34**	0.02 -0.86;0.86	-0.05 -0.86;0.75	**-0.64** **-0.91;-0.28**	**-6.31** **-11.16;-1.31**	-0.04 -0.78;0.17	-0.01 -1.05;0.79	-0.05 -1.60;0.89	0.6	0.2	0.8
Coping emotion-oriented	0.36 -1.97;2.71	1.03 -1.32;3.37	0.32 -0.04;0.73	**-3.69** **-7.40;-0.26**	-0.41 -1.12;0.15	**0.74** **0.14;1.35**	**-0.65** **-0.93;-0.27**	**-7.22** **-12.01;-2.53**	-0.07 -0.91;0.41	-0.15 -2.04;0.74	0.77 -0.76;3.39	1.1	2.3	11.9
Coping avoidance-oriented	0.36 -1.97;2.71	1.03 -1.32;3.38	0.32 -0.04;0.73	**-3.69** **-7.40;-0.26**	-0.41 -1.12;0.15	**0.74** **0.14;1.35**	**-0.65** **-0.93;-0.27**	**-7.22** **-12.01;-2.55**	-0.07 -0.91;0.41	-0.15 -2.04;0.74	0.77 -0.76;3.39	1.1	2.3	11.9

Table 8.4 continues on next page

Table 8.4 *Continued*

	Estimator (95% CI)								Estimator (95% CI)			% Mediation*		
	a_1	a_2	b_1	c'_1	b_2	b_3	d	c'_2	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$	$Path_{M1}$	$Path_{M2}$	$Path_{M3}$
Daytime sleepiness	-0.89 -2.67;0.74	-1.99 -3.78;0.16	**0.44 0.01;1.17**	-3.15 -6.82;0.38	-0.51 -1.14;0.22	**0.93 0.37;1.47**	**-0.54 -0.78;-0.22**	**-4.78 -9.40;-0.23**	0.21 -0.07;1.27	0.46 -0.26;2.27	**-1.84 -4.47;-0.23**	3.2	7.1	**28.4**
Concentration	**-2.76 -5.09;-0.43**	**-2.84 -5.64;-0.05**	0.29 -0.23;0.79	-2.88 -7.13;0.79	**-0.93 -1.45;-0.43**	**1.18 0.81;1.67**	**-0.57 -0.82;-0.27**	**-5.66 -9.86;-1.74**	0.45 -0.12;2.28	**2.55 0.42;5.85**	**-3.36 -7.36;-0.27**	6.9	**39.3**	**52.8**
Physical activities	**-2.64 -4.57;-0.75**	**-3.51 -6.04;-1.10**	**0.79 0.24;1.26**	-1.53 -5.42;1.68	**-0.84 -1.48;-0.34**	**1.43 0.97;1.80**	**-0.64 -0.87;-0.31**	**-3.71 -7.18;-0.21**	**1.34 0.30;3.71**	**2.22 0.51;5.84**	**-5.02 -9.24;-1.77**	**20.6**	**34.2**	**77.3**
Fear of disease progression	-0.96 -2.07;-0.11	0.49 -0.34;1.52	0.59 -0.85;1.91	-3.11 -6.82;0.95	-0.97 -3.56;2.07	-1.78 -4.43;1.10	**-0.67 -0.97;-0.28**	**-6.70 -11.61;-1.57**	0.38 -0.19;1.79	0.93 -1.24;4.98	-0.88 -5.42;0.51	5.9	14.3	13.6
Fatigue perception	-0.48 -3.81;2.72	**-4.08 -8.07;-0.42**	**0.29 0.02;0.59**	**-3.48 -6.98;-0.03**	-0.07 -0.45;0.27	**0.71 0.45;0.96**	**-0.64 -0.87;-0.35**	-3.80 -7.66;0.08	0.09 -0.52;0.96	0.04 -0.43;1.15	-2.88 -6.14;0.34	1.4	0.6	44.4
Depression	0.70 -0.86;2.08	0.10 -1.59;1.78	-0.22 -0.88;0.36	-3.47 -7.40;0.28	0.29 -1.21;1.56	0.10 -1.22;1.38	**-0.62 -0.90;-0.20**	**-6.49 -11.21;-1.89**	0.10 -0.11;1.29	0.20 -0.71;2.84	0.01 -1.00;1.48	1.5	3.1	0.2
Physical functioning	1.79 -3.91;7.69	2.07 -5.98;9.68	-0.07 -0.21;0.08	**-3.54 -7.24;-0.07**	0.05 -0.13;0.25	**-0.30 -0.53;-0.14**	**-0.64 -0.88;-0.36**	**-5.55 -10.31;-1.53**	0.08 -0.12;0.81	0.10 -0.25;1.56	-0.62 -4.28;1.37	1.2	1.5	9.6

* Estimator of mediated relation ($Path_{M1/M2/M3}$) / estimator c'_2 of the unmediated relation*100%.

Mediators during treatment

Most mediators acted via path c'_1 (CBT to $\Delta mediator_{baseline–T8}$ to $\Delta fatigue_{baseline–T8}$ to $\Delta fatigue_{T8–T16}$): more positive perception of fatigue (63.3%), increased level of physical activities (48.2%), increased physical functioning (33.1%), a reduction in daytime sleepiness (32.7%) and decreased helplessness (20.4%). The percentages represent the proportion of the total effect accounted for by the indirect effect per analysed possible mediator. Decreased daytime sleepiness (53.9%) also acted via path c'_2 (CBT to $\Delta mediator_{baseline–T8}$ to $\Delta fatigue_{T8–T16}$). None of the studied mediators were related via path c'_3 (CBT to $\Delta mediator_{T8–T16}$ to $\Delta fatigue_{T8–T16}$). The results of the longitudinal mediator analysis during the 16-week treatment period are displayed in Table 8.3.

Mediators of the change in fatigue after CBT

Most mediators acted via path c'_3 (CBT to $\Delta mediator_{T26–T52}$ to $\Delta fatigue_{T26–T52}$): more problems in being physical active (77.3%), more concentration problems (52.8%) and more daytime sleepiness (28.4%). Mediators for path c'_2 (CBT to $\Delta mediator_{T16–T26}$ to $\Delta fatigue_{T26–T52}$) were more concentration problems (39.3%) and more problems with being physically active (34.2%). More problems with physical activity (20.6%) acted via path c'_1 (CBT to $\Delta mediator_{T16–T26}$ to $\Delta fatigue_{T16–T26}$ to $\Delta fatigue_{T26–T52}$). The results of the analysed mediators after CBT (i.e. T16–T52) are displayed in Table 8.4.

Discussion

The primary analysis of the TREFAMS-CBT trial previously demonstrated the positive effect of CBT on MS-related fatigue.[Chapter 7] The current study showed that the mediating effect of most of the identified mediators, i.e. improved fatigue perception, increase in physical activities, improved physical functioning, a reduction in daytime sleepiness and decreased helplessness, was already present at week 8. These results are visualised in Figure 8.2. The TREFAMS-CBT trial also showed that after cessation of treatment the difference between CBT and the active control condition was no longer significant. Reduced levels of perceived physical activity, more concentration problems and increased daytime sleepiness mediated this unwelcome decline of the treatment effect, visualised in Figure 8.2B.

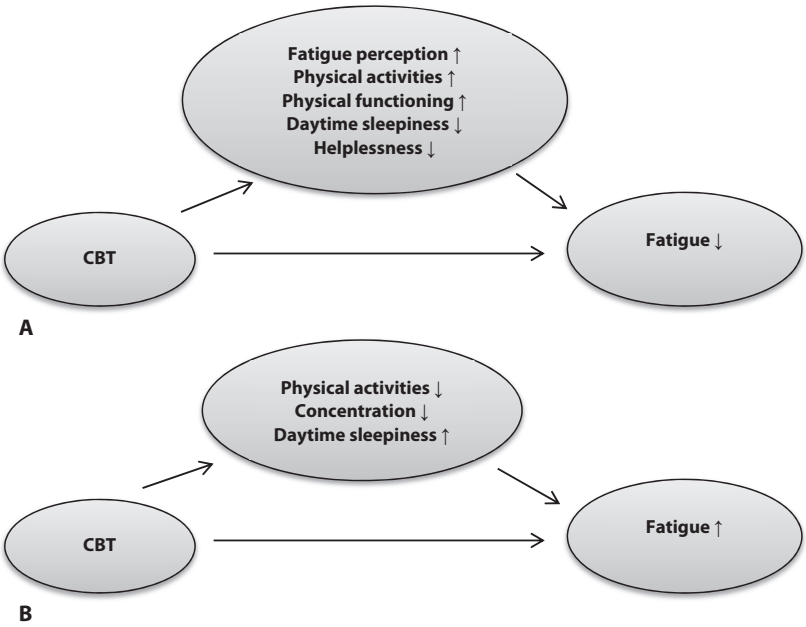


Figure 8.2 The effect of Cognitive Behavioural Therapy on MS-related fatigue with the significant mediators. **A.** During treatment. **B.** After treatment.

Mediators are most interesting when they can be modified with therapy. The identified mediators during therapy are directly and indirectly part of the treatment modules: changing beliefs regarding MS, regulating the sleep/wake cycle and regulating physical, mental, and social activities. The results of the current study hint at the effectiveness of these modules in the treatment of MS-related fatigue.

CBT aims for long-term behavioural change and a decrease in MS-related fatigue.[Chapter 7,21,42] The CBT and control intervention groups differed in terms of acquired skills, behaviours and cognitions. The mediators of an increase in fatigue after cessation of treatment were more concentration problems, more problems in being physically active, and more daytime sleepiness. These topics are at least partially treated during CBT. One focus of CBT was on the level of physical activity, i.e. a systematic increase in regular physical activity was strived for. Daytime sleepiness was likely influenced by the CBT module 'regulating sleep/wake pattern'. In this module the importance of good sleep hygiene and a regular sleep/wake rhythm is explained, and instructions and assignments are given on how this can be improved. Furthermore, the module 'regulation of mental activity' included helping participants learn how to deal with possible cognitive deficits

such as concentration. A suggested improvement in the long-term effectiveness of CBT on MS-related fatigue is to place more emphasis on long-term behavioural changes and the prevention of behavioural relapses during treatment.[42,43] Another approach might be to provide additional booster sessions after treatment that focus on improving concentration, increasing physical activity levels and decreasing daytime sleepiness. Concentration was measured with questions such as 'I can concentrate well', and 'my thoughts easily wander'. Therefore, this mediator should be interpreted as a subjective experience of concentration rather than objectively measured concentration, which is more closely related to cognitive disorders.

The present study showed the mediating effect of more positive fatigue perceptions and decreased helplessness. This is in line with previous research in patients with MS16 and chronic fatigue syndrome.[17,20] Two other CBT mediators in the current study were better physical functioning and more physical activities. This also agrees with previous research in patients with chronic fatigue syndrome.[17,19] One previously overlooked mediator that this study adds to the literature about the relation between CBT and MS-related fatigue is daytime sleepiness. The treatment module sleep/wake cycle did not specifically aim to decrease daytime sleepiness, but it might have influenced sleepiness due to the following advice: no daytime sleeping, just resting, and fixed times for sleep and waking. The relationship between mediators and fatigue is presumably not a simple linear cause-effect relationship but is more likely a continuous feedback loop with a reversed causal effect of fatigue outcome on the mediators.[17] Changing cognitions can lead to a decrease in fatigue, which might lead to further changes in cognitions and so on.[17]

Our study had some limitations that need to be considered. One limitation was the use in the TREFAMS-CBT study of measures that were mostly generic. Preferably one would use measures specific to the modules during CBT. For example, this might explain why *general* self-efficacy was not a mediator in this study: the CBT-treatment module aimed at improving *fatigue-related* self-efficacy. In line with this, we only used self-reported questionnaires of fatigue-related physical activities and physical functioning. Activity monitors might have resulted in different results, since there is a limited association between patient-reported physical activities and performance-based scores.[44-46] On the other hand, this study showed that CBT can influence perceived physical activities and physical functioning. This is related to improvements in MS-related fatigue over and above actual physical activities and physical functioning. It might be that a positive change in perceived physical limitations is itself enough to

improve MS-related fatigue. Another limitation was the relatively small sample size. The sample size for the TREFAMS-CBT trial was designed to allow detection of differences in clinical effectiveness between CBT and MS-nurse consultations, rather than analysis of mediation effects. Due to the small sample size the mediators had to be studied separately (univariate) as opposed to using multiple mediators together. Therefore, we were not able to draw conclusions on the relative contributions of mediators and their influence in relation to each other. Furthermore, the TREFAMS-CBT trial included an active control condition (MS-nurse consultations), which may also have influenced MS-related fatigue. It is important to bear in mind that the chosen study design allows one to measures only the additional effect of CBT on MS-related fatigue.

A key strength of the present study was the insight provided into factors related to changes in MS-related fatigue both during as well as after CBT. To the best of our knowledge, this is the first time the problem has been approached in this way. Another strength is that the studied models considered different paths in time. As shown in the results, some mediators were more conspicuous during certain periods. During treatment all mediators were related via the improvement of the mediators in the first 8 weeks ($\Delta mediator_{baseline-T8}$), except for sleepiness, which also worked via $\Delta mediator_{T8-T16}$. This might suggest that the largest improvements in both fatigue and mediators can be achieved during the baseline–T8 timeframe. A reduction in concentration problems between weeks 16 and 26 also mediated the reduction in fatigue, while the reduction in daytime sleepiness mediated the reduction in fatigue via all three paths, which emphasizes the importance of the latter mediator.

In conclusion, this study has shown that the following factors mediate the positive effect of CBT on MS-related fatigue: more positive fatigue perceptions, increased physical activity levels, improvement of physical functioning, reduced daytime sleepiness, and decreased feelings of helplessness. Furthermore, our results showed that the following factors are mediators after cessation of treatment: decrease in physical activity levels, a decrease in concentration and an increase in daytime sleepiness.

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